I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to:

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

On 15 Oct, 2003

TOWNSEND and TOWNSEND and CREW LLP

By: Malinda Adsit

PATENT
Attorney Docket No.: 018781-006210US
Client Ref. No.: T00-013-1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

LIN et al.

Application No.: 09/891,138

Filed: June 25, 2001

For: NOVEL RECEPTORS

Customer No.: 20350

Confirmation No.: 8826

Examiner: Christopher J. Nichols

Art Unit: 1647

DECLARATION UNDER 37 C.F.R. 1.132 BY DANIEL LIN, PH.D.

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

1. I, Daniel Lin, Ph.D., am a scientist at Tularik Inc., a biopharmaceutical company headquartered in South San Francisco, CA and the assignee of the above-referenced patent application. I am the inventor of the subject matter disclosed and claimed in the above-referenced patent application.

2. I hold a Ph.D. from the Massachusetts Institute of Technology (1999). I have worked in the field of G protein-coupled receptors for about four years.

3. It is my understanding that the claims currently under xamination, which relate to, *inter alia*, murine TGR18 nucleic acid sequences, were rejected as allegedly lacking utility. This

Declaration presents exemplary data showing that TGR18 functions as a GPCR. The experiments were performed by myself or under my supervision.

4. GPCR activity can be assessed using a variety of common assays. One such assay is an Aequorin assay. Aequorin assays are widely used in the art to measure GPCR-mediated increases in intracellular calcium. The assay involves the use of the Ca^{2+}-sensitive photoprotein aequorin. The aequorin complex contains the apo-aequorin protein, molecular oxygen, and the luminophore coelenterazine. The binding of calcium ions disrupts the complex, leading to the emission of blue light, which provides a means of determining increases in intracellular calcium.

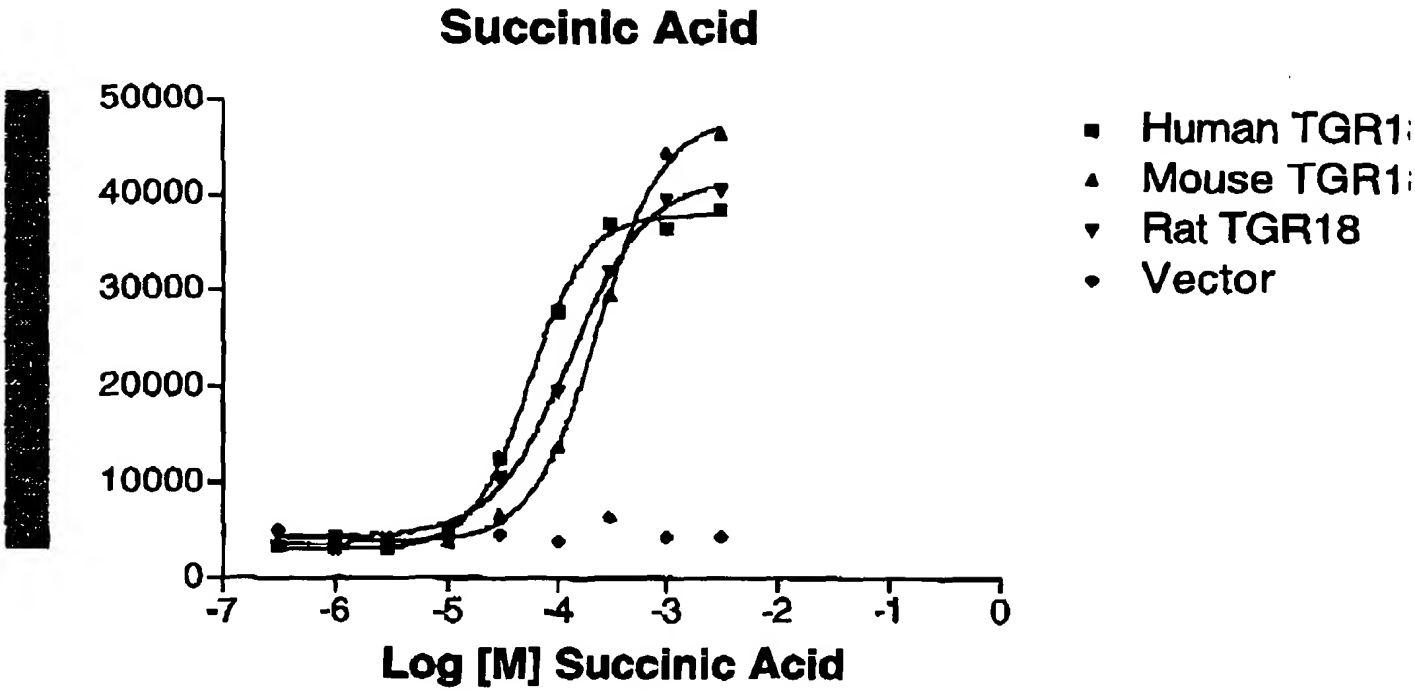
5. Mouse, human, and rat TGR18 GPCR activities were tested in an Aequorin assay. Briefly, CHO cells were transiently co-transfected with 10 μg of an Aequorin reporter gene and 10 μg of a cDNA encoding human TGR18, mouse TGR18, rat TGR18, or a vector control. Th mouse TGR18 expression vector comprises the coding region of the cDNA sequence presented in SEQ ID NO:1, which encodes the protein of SEQ ID NO:2. Following transfection, the cells were harvested and re-suspended in buffer containing coelenterazine f. Aequorin luminescence was determined following incubation of the harvested cells with ligand. The results, shown in Figure 1, demonstrate that mouse, human, and rat TGR18 all have GPCR activity: they each transduce an increase in intracellular calcium.

6. I further declare that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both (18 U.S.C./1001), and may jeopardize the validity of the patent application or any patent issuing thereon.

Date: Oct 15, 2003 By: _____

Daniel Lin, Ph.D.

Figure 1


Succinic Acid
50000
40000
30000
20000
10000
0
-7
-6
-5
-4
-3
-2
-1
0
Log [M] Succinic Acid
Human TGR1
Mouse TGR1
Rat TGR18
Vector